

### REMARKS

In response to the office action ("Office Action") mailed March 26, 2007, Applicants have canceled claims 1-8 and 11-21, and added new claims 22-26. Support for new claims 22-26 can be found in original claim 1. No new matter has been introduced by the above amendments.

Claims 22-26 are currently pending. Reconsideration of this application, as amended, is requested in view of the following remarks.

#### Rejection under 35 U.S.C. § 112, 1<sup>st</sup> paragraph

The Examiner rejects claims 1-6 and 12-21 under 35 U.S.C. § 112, 1<sup>st</sup> paragraph on two grounds. Applicants have cancelled claims 1-6 and 12-21 and will traverse each ground against new claims 22-26 as follows:

#### I

Claims 1-6 and 12-21 are rejected on the ground that "the specification does not contain description of the invention, and of the manner and process of making and using the invention, to enable any person skilled in the art to which it pertains." See the Office Action, page 2, lines 14-17. Specifically, the Examiner indicates that "[e]xamples of evidence of lack of enablement are in the description for the preparation of a carboxylic acid, INTERMEDIATE 6 (page 24 of [the] specification) and the written description of the preparation of an amide, EXAMPLE 8 (page 27 of [the] specification)." See the Office Action, page 2, lines 17-20. It appears to be the Examiner's position that the specification (1) does not provide an enabling description for the preparation of INTERMEDIATE 6 and (2) does not provide an adequate written description for the preparation of EXAMPLE 8. Applicants traverse each of these two alleged deficiencies below:

(1) The Examiner contends that "[t]he preparation of the INTERMEDIATE 6 [page 24 of the specification], allegedly, involves heating in an autoclave, a solution of an aryl bromide in methanol and triethylamine to 90°C for 17h in carbon monoxide at 6 bar. The outcome of the reaction is said to be replacement of bromide radical in the aryl bromide by a CO<sub>2</sub>CH<sub>3</sub> moiety. This is an uncommon, unique reaction because such transformation usually require the use of organo-metallic catalysts. This was not disclosed in the specification." See the paragraph

bridging pages 2 and 3 in the office action. Applicants would like to point out that, due to a clerical error, the Specification incidentally omits an organometallic catalyst in the description of the preparation of Intermediate 6 on page 24. However, one skilled in the art could readily recognize this error and would consult literature (as suggested by page 10, lines 6-7 of the specification) for clarification. Indeed, it appears that the Examiner was able to do so without any difficulty. In addition, the Specification only describes one method of preparing Intermediate 6 on page 24. The Specification also indicates that the intermediates disclosed therein, including Intermediate 6, can be prepared by other methods known in the art. See, e.g., page 10, lines 6-7. Thus, one skilled in the art would know how to prepare Intermediate 6, a relative simple compound, regardless of the error in the description on page 24. Thus, pending claims 22-26 are enabled by the Specification.

(2) The Examiner asserts that “[a]mides, in general, are formed by the reaction of carboxylic acid and amine in the presence of a coupling agent and tertiary amine catalyst. However, the written description claims to have produced amides without using any carboxylic acids.” See the Office Action, page 2, lines 17-20. Again, Applicants would like to point out that the Specification omits a carboxylic acid in the description of the preparation of Example 8 due to a clerical error. However, even in view of this error, one skilled in the art could readily understand that Applicants had successfully prepared Example 8 and therefore had possession of this compound. Indeed, the paragraph immediately following the description of the preparation of Example 8 on page 27 states that “[t]he following Examples were prepared analogously to Example 8 from the appropriate acids and amines.” See page 27, lines 15-16; emphasis added. In view of this statement, one skilled in the art can readily understand that Example 8 were prepared from an acid and an amine. Further, the description on page 27 provides that Example 8 is methyl 2-[[4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidinyl]carbonyl]-4-methoxybenzoate and the amine used as a starting material for preparing Example 8 is 4-(3,4-dichlorophenoxy)-1-(4-piperidinylmethyl)-piperidine. From the chemical structures of Example 8 and the amine, one skilled in the art can readily understand that the appropriate acid used to prepare Example 8 must be methyl 2-carboxyl-4-methoxybenzoate. In addition, the description on page 27 states that Example 8 was purified by RPHPLC and its chemical structure was confirmed by mass spectroscopy. Thus, one skilled in the art could understand that Applicants

had successfully prepared Example 8 and therefore had possession of this compound. In sum, the specification provides an adequate written description for the preparation of Example 8.

For the reasons set forth above, Applicants request withdrawal of this rejection.

## II

Claims 1-6 and 12-21 are rejected as being non-enabled on the ground that "the specification, while being enabling for few limited class of amide[] compounds, does not reasonably provide enablement for the generic class of amide compounds." See the Office Action, page 3, lines 9-11. Applicants have cancelled claims 1-6 and 12-21, and added new claims 22-26. Thus, Applicants will only discuss this rejection in view of the new claims. Independent claim 22 is discussed first.

In support of his enablement rejection, the Examiner has considered all of the Wands factor and has focused on the following five most relevant factors: (1) the breadth of the claims, (2) the amount of direction provided by the inventor, (3) the presence or absence of working examples, (4) the quantity of experimentation, and (5) the relative skill of those in the art. Applicants traverse each factor below:

**(1) The breadth of the claims:** The Examiner contends that "the claims are very broad." Specifically, the Examiner states that

"Claims 1-6 and 12-21 are drawn to carboxylic amides, derived from a piperidine (amine) portion and a carboxylic acid (acid) portion. The amine portion has five main variables. The acid portion comprises of compounds derived from substituted aryl and substituted heteroaryl groups connected to the carboxylic group by bond, CH<sub>2</sub>, or CH<sub>2</sub>O. The substitutions on the aryl and heteroaryl groups include plurality of functionalities comprising OH, CO<sub>2</sub>R<sup>3</sup>, CH<sub>2</sub>CO<sub>2</sub>R<sup>3</sup>, CH<sub>2</sub>SO<sub>3</sub>H, OCH<sub>2</sub>CO<sub>2</sub>R<sup>3</sup>, ... OCH<sub>2</sub>SO<sub>3</sub>H, hydrogen, halogen, cyano, nitro, hydroxyl, NR<sup>4</sup>R<sup>5</sup>C<sub>1-6</sub> alkyl (optionally substituted with halogen), C<sub>1-6</sub> alkoxy (optionally substituted with halogen), S(O)<sub>p</sub>(C<sub>1-6</sub> alkyl), S(O)<sub>q</sub>CF<sub>3</sub>, or S(O)<sub>q</sub>NR<sup>4</sup>R<sup>5</sup>; p and q being 0, 1, 2, and each R group further containing additional variables." See the Office Action, page 4, lines 4-13.

Applicants have substantially narrowed original claim 1 and rewritten the narrowed claim 1 as claim 22. For example, the acid portion of the compounds of formula (I) recited in claim 22 only includes substituted phenyl groups, not substituted aryl or heteroaryl groups as indicated in the Examiner's statement above. Further, the substituted phenyl group is connected to a

carbonyl group only via a bond, not via  $\text{CH}_2$  or  $\text{CH}_2\text{O}$  as indicated by the Examiner. In addition, the substitutions on the phenyl group has been limited to specific groups, i.e., hydrogen, halogen, cyano,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  alkoxy,  $\text{CF}_3$ ,  $\text{OCF}_3$ ,  $\text{S}(\text{O})_2(\text{C}_{1-4} \text{ alkyl})$ , or  $\text{S}(\text{O})_2\text{NH}_2$ , the number of which are substantially smaller than that of the substituents on the corresponding aryl or heteroaryl groups of the acid portion of the compounds of original claim 1. In view of the above amendments, Applicants submit that claim 22 is not broad.

**(2) The amount of direction:** The Examiner asserts that

"The questionable description of INTERMEDIATE 6 (page 24) and EXAMPLE 8 (page 27) is mentioned above. In addition, the amount of direction provided by the specification for making the above mentioned 'amine' part is limited to  $\text{Q} = \text{H}$ ; and  $\text{W} = \text{CH}_2$  or  $\text{O}$  and is not applicable when  $\text{Q} = \text{OH}$  or When  $\text{R}_2$  is  $\text{H}$ . The direction provided by the specification for making the above mentioned 'acid' part is limited to  $\text{Y} = \text{CO}_2\text{H}$ ,  $\text{CH}_2\text{CO}_2\text{CH}_3$ ." See the Office Action, page 4, lines 16-21.

As discussed above, claim 22 is adequately enabled by the Specification even in view of the description of INTERMEDIATE 6 and EXAMPLE 8. Further, Applicants have limited  $\text{Q}$  recited in claim 22 to  $\text{H}$  and limited  $\text{W}$  recited in claim 22 to  $\text{O}$ , thereby excluding  $\text{OH}$  as a group assigned to  $\text{Q}$  and  $\text{NR}^2$  as a group assigned to  $\text{W}$ .

Moreover, Applicants would like to point out that the Examiner clearly erred in stating that "the direction provided by the specification for making the above mentioned 'acid' part is limited to  $\text{Y} = \text{CO}_2\text{H}$ ,  $\text{CH}_2\text{CO}_2\text{CH}_3$ ." Indeed, the specification already describes preparation of compounds in which  $\text{Y}$  is  $\text{CO}_2\text{H}$  (see, e.g., Examples 1-5 and 13-17),  $\text{CH}_2\text{CO}_2\text{CH}_3$  (see, e.g., Example 6),  $\text{CO}_2\text{CH}_3$  (see, e.g., Example 7),  $\text{CH}_2\text{CO}_2\text{H}$  (see, e.g., Example 12), and  $\text{OH}$  (see, e.g., Example 19). In any event, Applicants have limited  $\text{Y}$  recited in claim 22 to  $\text{OH}$ ,  $\text{CO}_2\text{R}^3$ , or  $\text{CH}_2\text{CO}_2\text{R}^3$ , in which  $\text{R}^3$  is hydrogen or  $\text{C}_{1-6}$  alkyl. Of note, given that the Specification already describes preparing specific compounds in which  $\text{Y}$  is  $\text{CO}_2\text{R}^3$  or  $\text{CH}_2\text{CO}_2\text{R}^3$  and  $\text{R}^3$  is hydrogen or methyl, one skilled in the art would readily understand how to make compounds in which  $\text{R}^3$  is an alkyl group recited in claim 22 other than methyl.

In sum, Applicants submit that the specification provide adequate direction for preparing the compounds of claim 22.

**(3) The presence or absence of working examples:** The Examiner contends that

"The Examples indicated in the specification are applicable to compounds wherein  $Y = CO_2H$ ,  $CH_2CO_2CH_3$ ;  $Q = H$ , and  $W = CH_2$  or  $O$ . There are no working examples for  $Y =$  sulphur containing variables. There are no working examples for  $Q = OH$ . There is one example of a heteroaryl carboxamide, 'prepared' by the above-mentioned method of EXAMPLE 8. There are no working examples of formation of N-oxides, pharmaceutically acceptable salts and/or solvates thereof." See the Office Action, page 5, lines 1-7.

As mentioned above, Applicants have limited claim 22 to compounds in which  $Q$  is  $H$ ;  $W$  is  $O$ ; and  $Y$  is  $OH$ ,  $CO_2R^3$ , or  $CH_2CO_2R^3$ . In other words, Applicants have excluded sulfur containing groups from  $Y$  and excluded  $OH$  from  $Q$ . Applicants have also limited claim 22 to compounds in which  $E$  is  $CH$ , thereby excluding heteroaryl carboxamide compounds from this claim. Finally, Applicants have excluded recitation of N-oxides, pharmaceutically acceptable salts and/or solvates from claim 22. In view of the above amendments, Applicants submit that claim 22 is fully supported by the working examples in the specification.

Further, Applicants would like to bring to the Examiner's attention that "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed," and "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." See MPEP 2164.02. In other words, no example is required if a specification already provides adequate guidance to practice an invention. The present specification already provides adequate general guidance on how to prepare the compounds of formula (I) (see, e.g., page 7, line 22 to page 10, line 16) and how to use these compounds (see, e.g., page 10, line 19 to page 21, line 24). In view of the specification, one skilled in the art would have readily understood how to prepare and use all compounds of claim 22 without undue experimentation. Thus, Applicants submit that the specification would have enabled claim 22 even without any working example.

(4) **The quantity of experimentation:** The Examiner asserts that "[t]he lack of working examples for formation amides from aryl and heteroaryl carboxylic acids with complex groups, such as  $CH_2SO_3H$  or  $OCH_2SO_3H$ , and lack of citation of sources for the functionalized starting material 'amines' and 'carboxylic acids' would require a burdensome amount of research for one skilled in the art to practice the invention." See the Office Action, page 5, lines 8-12.

Applicants have excluded complex substituents on the acid portion (such as  $\text{CH}_2\text{SO}_3\text{H}$  or  $\text{OCH}_2\text{SO}_3\text{H}$ ) from the compounds of claim 22. Further, as discussed above, no working example is required if a specification already provides adequate guidance to practice an invention. Since the present specification already provides adequate general guidance on how to prepare and use the compounds of formula (I) of claim 22, it enables this claim even though it does not provide working examples of every compound covered by this claims. In addition, the starting materials for preparing the compounds of claim 22 either are commercially available or can be readily prepared from commercially available compounds by methods well known in the art. Thus, Applicants submit that no burdensome amount of research is required for one skilled in the art to practice the compounds covered by claim 22.

(5) **The relative skill of those in the art:** The Examiner states that “the skill of one of ordinary skill in the art is very high, e.g., Ph.D. and M.D. level technology.” See the Office Action, page 5, lines 13-14. The Examiner appears to assert that practicing the claimed invention requires a person with a high level of skills, such as a Ph.D. or M.D. Applicants would like to point out that a Ph.D. or M.D. is a person of ordinary skill in this art. Further, the techniques needed to practice the claimed invention are synthesizing a compound of claim 22 and testing it in an assay known to be correlated to clinical efficacy for treating a disease described in the specification. These techniques were well known at the time the invention was made and therefore do not require a Ph.D. or M.D. of extraordinary skill.

In view of the remarks above, Applicants submit that claim 22 is enabled by the present specification. So are claims 23-26, all of which depend from claim 22. Accordingly, Applicants request withdrawal of this rejection.

### CONCLUSION

Applicants submit that the grounds for rejection asserted by the Examiner have been overcome, and that claims 22-26, as pending, define subject matter that is sufficiently described and enabled. On this basis, it is submitted that all claims are now in condition for allowance, which action is requested.

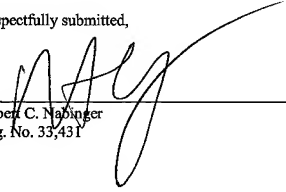
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Respectfully submitted,

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